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Anticholinergic Burden Measures Predict Older People's Physical Function and Quality of Life: A Systematic Review

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Abstract:	Phyo Kyaw Myint, MD
	Objectives: This systematic review (PROSPERO CRD42019115918) compared the evidence behind anticholinergic burden measures and their ability to predict changes in older people's physical function and quality of life.
	Design: Eligible cohort or case-control studies were identified systematically using comprehensive search terms and a validated search filter for prognostic studies. Medline (OVID), EMBASE (OVID), CINAHL (EMBSO) and PsycINFO (OVID) databases were searched. Risk of bias, using Quality in Prognosis Studies tool, and quality of evidence, using GRADE, were assessed.
	Setting and Participants: People aged 65 years and older from any clinical setting.
	Measures: Any anticholinergic burden measures were accepted (including the anticholinergic domain of the Drug Burden Index). Any global/ multi-dimensional measure for physical function and/ or quality of life was accepted for outcome.
	Results: Thirteen studies reporting associations between anticholinergic burden and physical function (n=10) or quality of life (n=4) were included. Exposure measures included; Anticholinergic Cognitive Burden Scale, Anticholinergic Drug Scale, Anticholinergic Risk Scale, Clinician Rated Anticholinergic Score and the anticholinergic domain of the Drug Burden Index. All studies were rated moderate risk of bias in ≥ 2 QUIPS categories with five rated high risk in ≥ 1 categories. Seven of ten studies (5,251 of 7,569 participants) reported significant decline in physical function with increased burden. All four studies (2,635 participants) reporting quality of life demonstrated similar association with increased burden. High risk of biases and inadequate data reporting restricted analysis. There was no evidence to support one measure being superior to another.
	Conclusions and Implications: The evidence supports association between increased anticholinergic burden and future impairments in physical function and quality of life. No conclusion can be made regarding which ACB measure has the best prognostic value. Well-designed longitudinal studies are required to address this. Clinicians should be aware of patient's

	anticholinergic burden and consider alternative medications where appropriate.
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**Title: Anticholinergic Burden Measures Predict Older People's Physical Function and Quality of Life:
A Systematic Review**

Running Title: Anticholinergic Burden and Older People's Function and Quality of Life

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Brief Summary:

Our systematic review demonstrated that anticholinergic burden was associated with impairments of physical function and quality of life, but no anticholinergic burden measure was superior to another.

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Design: Eligible cohort or case-control studies were identified systematically using comprehensive search terms and a validated search filter for prognostic studies. Medline (OVID), EMBASE (OVID), CINAHL (EMBSO) and PsycINFO (OVID) databases were searched. Risk of bias, using Quality in Prognosis Studies tool, and quality of evidence, using GRADE, were assessed.

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Results: Thirteen studies reporting associations between anticholinergic burden and physical function (n=10) or quality of life (n=4) were included. Exposure measures included; Anticholinergic Cognitive Burden Scale, Anticholinergic Drug Scale, Anticholinergic Risk Scale, Clinician Rated Anticholinergic Score and the anticholinergic domain of the Drug Burden Index. All studies were rated moderate risk of bias in ≥ 2 QUIPS categories with five rated high risk in ≥ 1 categories. Seven of ten studies (5,251 of 7,569 participants) reported significant decline in physical function with increased burden. All four studies (2,635 participants) reporting quality of life demonstrated similar association with increased burden. High risk of biases and inadequate data reporting restricted analysis. There was no evidence to support one measure being superior to another.

Conclusions and Implications:

The evidence supports association between increased anticholinergic burden and future impairments in physical function and quality of life. No conclusion can be made regarding which ACB measure has the best prognostic value. Well-designed longitudinal studies are required to address this. Clinicians should be aware of patient's anticholinergic burden and consider alternative medications where appropriate.

Introduction

Physical function and quality of life are two important health outcomes for older people.¹ Physical function focuses upon an individual's activities and participation, particularly in relation to what would be considered normal general daily tasks, self-care activities, and participation in community and social interactions.² Quality of life overlaps this, defined as "*a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment*".³ Quality of life is concerned more with the impact of activity and participation limitations upon well-being.⁴ Both outcomes are considered key research priorities by both older people and health professionals.¹

Understanding what influences these outcomes is important; factors which are modifiable can be targeted to improve older people's physical function and quality of life. One potentially important factor is anticholinergic burden (ACB)⁵⁻⁶ the accumulation of anticholinergic effects from one or more anticholinergic medications.⁷⁻⁸ Medications with anticholinergic properties are prescribed for a range of common problems in older age, including urinary incontinence, depression and gastrointestinal complaints.⁸⁻⁹ Side-effects include confusion, constipation, delirium, dizziness, drowsiness and dry mouth.⁸⁻⁹ Studies estimate up to 50% of community dwelling older adults use one or more anticholinergic medications.¹⁰⁻¹¹ However, in addition to being the greatest consumers of anticholinergic medications, older people are more susceptible to side effects and adverse outcomes.⁸ To date, while a number of reviews in this area have included older people, few reviews have specifically restricted inclusion and

analysis to older people. Therefore there is an urgent need to understand anticholinergic use and its consequences within the older adult population.

Several factors presently limit advancing knowledge in this area, not least study design and choice of ACB measure. Our previous (unpublished) research identified fourteen ACB measures reported in the literature. The variation in ACB measures makes interpretation challenging; the ACB measures differ substantially.¹²⁻¹³ The number of medications assessed in each scale varies from 27 in the Anticholinergic Burden Classification, to 117 in the Anticholinergic Drug Scale.¹³ The potency score for individual medications also varies between scales.¹³ For example, Nortriptyline is rated as having high anticholinergic activity by Boustani *et al.*, (2008) in the Anticholinergic Cognitive Burden Scale¹⁴ but moderate by Rudolph *et al.*, (2008) in the Anticholinergic Risk Scale¹⁵. As yet no evidence provides clear rationale to support use of one measure above another. Additionally, many reviews have included cross-sectional study designs, restricting our understanding of the temporal relationship between ACB and future outcomes. There is a need to explore the ability of individual ACB measures to predict these outcomes and identify if one ACB measure performs better than another. Understanding the prognostic utility of ACB measures will enhance future outcome reporting for trials seeking to reduce ACB.

This systematic review aims to:

- describe the association of individual ACB measures with physical function and quality of life, and

- compare the prognostic utility of ACB measures.

Methods

This PROSPERO registered systematic review (CRD42019115918, available: <http://www.crd.york.ac.uk/PROSPERO>) was conducted using the Cochrane Prognostic Review Group Framework for Prognostic Reviews (<https://methods.cochrane.org/prognosis/our-publications>)¹⁶ and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (**see supplementary file 1 for PRISMA checklist**).

Literature search strategy

The search strategy was developed following extensive scoping searches to identify appropriate MeSH and other controlled vocabulary for ACB and ACB measures. We employed a validated search filter for the identification of prognostic studies.¹⁷ The strategy was modified to suit each database searched (MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO) and PsycINFO (Ovid)). Searches were from 1st January 2006 to 4th March 2020. The 2006 inception was chosen as the time when ACB was first conceptualised and studied. The full strategy is reported in our **supplementary file 1**.

Inclusion criteria

The following criteria were applied to identify appropriate studies:

- Report a prospective or retrospective observational study (longitudinal cohort or case-control)
- Involve adults aged ≥ 65 years (or mean age ≥ 65 years)
- Assess ACB exposure using any ACB measure (to include anticholinergic (Ach) domain of the Drug Burden Index (DBI))
- Any length of follow-up period
- Report any global/ multi-dimensional measure of physical function and/ or quality of life as an outcome

Exclusion criteria

The following exclusion criteria were applied:

- Studies restricted to measuring classes of or specific anticholinergic medications (e.g. psychotropics)
- Measure of medications not specifically directed at anticholinergic drugs (e.g. Beers criteria)

Study selection process

Searches were conducted on the 16th November 2018, then updated on 4th March 2020 and identified studies transferred to Covidence systematic review software ©2019 (Veritas Health Innovation Ltd., www.covidence.org). After duplicates were removed, 13,394 studies remained. These were then screened by title and abstract by two independent reviewers (shared between CS, KY, MK). Both primary reviewers had to agree upon exclusion and, where

this was not the case, a third independent reviewer made the final decision (TQ). The full text of remaining studies (n=124) were screened by two independent reviewers (shared between CS, KY, MK). Again, a third independent reviewer resolved any disagreements (TQ). Exclusion reasons are reported in the identified PRISMA flow chart (Supplementary file). Reference lists of included studies were searched, and citations via PubMed reviewed, to check for studies our search had omitted. Reference lists and citations of recent seminal articles^{13,18} were also searched. No additional studies for inclusion were identified. Thirteen articles remained which reported physical function or quality of life as an outcome.

Data collection and extraction

A data extraction template was developed in accordance with guidance by the Cochrane Prognostic Review Group framework (<https://methods.cochrane.org/prognosis/our-publications>).¹⁶ This included study characteristics (e.g. year of publication, country, study setting), measures assessed, timing and methods of assessments, statistical plan, confounders/ adjustments and results. Two reviewers (shared between CS, KY, MK) independently extracted data and a third reviewer arbitrated any disagreements (TQ). Data were then transferred to a Microsoft Excel 2016 (<https://products.office.com/en-gb/excel>) sheet and imported to Comprehensive Meta-Analysis v3.3.070 (<https://www.meta-analysis.com/>) for analysis.

Risk of bias

Risk of bias for each included study was assessed using the Quality in Prognosis Studies tool, developed by the Cochrane Prognosis Methods Group (QUIPS, available: <https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf>).¹⁹ Risk of bias is assessed across six domains: study participation, attrition, prognostic measurement, outcome measurement, study confounding and statistical analysis. As recommended, we took the QUIPS anchoring statement and modified the wording to suit our review question. We agreed to accept any baseline measure of ACB and for statistical analysis we agreed within the research team a minimum level of adjustment (set of confounders) that would constitute high quality (discussed further below). Assessments were conducted by those who completed data extraction (CS, KY, MK) and any disagreements arbitrated by a third reviewer (TQ). Publication bias was planned to be assessed by way of funnel plot.

Analysis

All included studies underwent narrative analysis following the guidance provided by the European Social Research Council.²⁰ Findings were assessed qualitatively considering clinical heterogeneity and the risk of biases. Patterns of associations across the studies were also explored and described. Association data extracted included odds ratios, risk ratios, their respective confidence intervals, β values, standard error and p values, where reported. Baseline and follow-up scores for ACB and relevant outcome were recorded if reported. Pooled analysis was planned with summary statistics where possible for both adjusted and unadjusted data.

Which factors and what constitutes minimum adjustment was determined by consensus, using a Delphi approach involving the senior authors (CS, RLS, YKL, PKM). It was agreed after one round that minimum adjustment would be age and sex and ≥ 1 co-morbidities (or a global measure of the number of co-morbidities). Where possible forest plots and meta-analyses using random effects modelling techniques were planned to graphically and statistically demonstrate the body of evidence. Results were analysed according to our hierarchy of research questions:

- Prognostic utility of individual ACB measures for each outcome of interest (all measures for either physical function or quality of life combined)
- Comparison of prognostic utilities of ACB measures for each outcome of interest (all measures for either physical function or quality of life combined)

Quality assessment

The GRADE assessment tool was used to determine the quality of the body of evidence for each scale and outcome. The GRADE approach assesses the evidence across all studies analysed for a given outcome, rather than assessing the evidence from each study individually.²¹ The GRADE framework allows the quality of the evidence to be judged across criteria known to limit the quality of evidence.²¹ Guidance for applying GRADE to prognostic studies was taken from Huguet *et al.* (2013).²² Quality was assessed across seven criteria; study limitations, inconsistency, indirectness, imprecision, publication bias, effect size and dose-effect. Further details regarding these criteria can be found on the GRADE website [<http://www.gradeworkinggroup.org>].

Results

Of the 13 studies²³⁻³⁵, ten reported associations between ACB and physical function^{23,24,26,27,29-34} and four reported associations with quality of life^{23,25,28,35}. One study²³ is reported twice as it reports both outcomes. Five measures for ACB exposure were included; Anticholinergic Cognitive Burden Scale, Anticholinergic Drug Scale (modified- Clinician Rated Anticholinergic Score), Anticholinergic Risk Scale, Clinician Rated Anticholinergic Score, and the anticholinergic domain of the Drug Burden Index. Each scale was developed within the United States of America. The Anticholinergic Cognitive Burden Score assesses 88 medications considered by expert opinion to have anticholinergic properties which have significant impact upon cognition.²⁴ The Anticholinergic Drug Scale assesses 117 medications which are scored based on each medications serum anticholinergic activity as published in the existing literature.^{13,35} The Anticholinergic Drug Scale was originally known as the modified Clinician Rated Anticholinergic Score.¹³ The Anticholinergic Risk Scale assesses 49 medications considered to have anticholinergic properties which have significant impact on both cognitive and physical function.²⁴ The Clinician Rated Anticholinergic Score assess 60 medications, identified from several ACB scales, considered strongly implicated in the development of delirium.^{13,26} The anticholinergic domain of the Drug Burden Index is somewhat different from other ACB measures in that it considers dose and duration of use of individual anticholinergic medications.²⁸ It was also developed based upon existing literature and expert opinion.²⁸

Physical function

Descriptive details for each study are presented in table 1. In total 7,569 older people participated across the ten studies, with mean (+/-SD) ages ranging from 71.9 (12.0) years²³

to 86.1 (6.8) years.²⁹ Three studies were conducted in Italy ^{24,32,34}, three in the USA ^{26,29,31} and one each from Australia ²³, Israel ²⁷, Spain ³³ and the U.K. ³⁰

Table 2 Characteristics of studies reporting association between ACB and physical function (n=10) and quality of life (n=4)

Risk of bias for each study (n=10) is presented in Figure 1. Of the ten studies, four papers were considered high risk of bias ≥ 1 QUIPS categories.^{23,29,31,34} High risk of bias arose most commonly from issues around participation, including poor descriptions of sample group²³, inadequate description of those excluded³¹ or little information regarding participation rate.²⁹ Moderate risks of bias were common throughout all studies; attrition (the number, reasons for or exploration of outcome factors in those lost) was rarely addressed. A funnel plot for assessing publication bias was not possible due to variation in statistical effect sizes presented and too few studies.

Fig. 1. QUIPS Risk of bias assessment of studies reporting association between ACB and physical function (n=10) and quality of life (n=4)

Anticholinergic Cognitive Burden Scale (ACBS) and physical function

Six studies, with sample sizes ranging from n=99²⁹ to n=1429³¹ explored the relationship between baseline ACB and future physical function using the ACBS (See table 2). Three studies

reported significant associations between increased ACB and impaired physical function^{24,29,31} with little difference between un-adjusted and adjusted results. Brombo 2018²⁴ reported the strongest association between increased ACBS score and a decline in Activities of Daily Living scores (2.77, 95% CI 1.39,5.54). Inconsistencies between studies regarding statistical analysis and data presented limited further analysis. For example, as shown in table 2 the six studies utilised four different physical function outcome measures and varied in comparison groups (e.g. ACBS=0 v ACBS ≥1 or ACBS≤1 v. ACBS ≥2).

Table 2 Summary of results for studies reporting impact of ACB upon physical function (n=10)

Anticholinergic Risk Scale (ARS) and physical function

Four studies with sample sizes ranging from n=105³⁰ to n=1490³² explored relationships between ACB and physical function using the ARS (table 2). Studies varied in statistical analysis and findings; two of four studies reported significant association between baseline ARS and future functional decline.^{30,32} Notably, Brombo 2018²⁴, in contrast to their findings using the ACBS, failed to find a positive association between function and ACB using the ARS measure (OR 1.49, 95% CI 0.60, 3.70).

Clinician Rated Anticholinergic Score (CRAS) & modified Clinician Rated Anticholinergic Score (mCRAS) and physical function

Two studies explored relationships between ACB and physical function using the CRAS or mCRAS.^{23,26} Sample sizes ranged from n=461²³ to n=544²⁶. Agar (2009)²³ reported an OR 0.85

(95% CI 0.81, 0.90) between the baseline CRAS of older palliative care patients and a decrease in Australian-modified Karnofsky Performance Status (AKPS) category; those with higher ACB were less likely to be classed as independent at follow-up. Han (2008)²⁶ reported an effect estimate of 0.10 (95% CI 0.04, 0.17) suggesting for every unit increase in mCRAS score there is a 10% reduction in IADL (i.e. lower independence).

Comparison of prognostic ability of ACB measures to predict future physical function

Only two studies directly compared >1 ACB measures in the same population; Brombo (2018)²⁴ and Pasina (2013)³⁴ both compared the ACBS and ARS abilities to predict future physical function. Brombo (2018)²⁴ reported associations with the ACBS but not ARS, while Pasina (2013)³⁴ failed to find a significant relationship with either the ACBS or ARS.

Quality of Life outcome studies

In total 2,635 older people participated across the four studies, with mean (SD) ages ranging from 71.0 (12.0) years²³ to 78.6 (6.7) years²⁸. Two studies were conducted in the U.S.A.^{28,35} and one each from Australia²³ and Canada.²⁵ Further details of each study are presented in table 1.

Risk of bias for each study (n=4) is presented in Fig. 1. Of the four studies, two papers were considered high risk of bias in ≥ 1 QUIPS categories.^{23,35} High bias risks arose from a lack of reporting of, or adjustment for, confounders and unclear analysis plans.^{23,35} Moderate risks of bias were common throughout; Participation rates were rarely reported, the number,

reasons for or exploration of those lost to follow up was rarely addressed, along with non-reporting of missing data. A funnel plot for assessing publication bias was not possible due to variation in statistical effect sizes presented and too few studies.

ACBS and quality of life

Two studies, with sample sizes ranging from $n=426^{28}$ to $n=1793^{25}$ explored the relationship between baseline ACB and quality of life using the ACBS. Table 3 summarises results. Cossette (2017) identified a significant association between baseline ACB and the physical domain of the SF36 (β -0.50 (95% CI -0.31, -0.68) $p<.001$) but not the mental domain (β 0.19 (95% CI 0.01,0.37) $p=ns$).²⁵ Conversely, using the EQ5D, le (2017) did not identify any association with ACBS score over 12 months (β 0.006 (95% CI -0.01 to 0.02) $p=ns$).²⁸ Cossette (2017) do not present results combining the domains of the SF36 making it difficult to compare the two sets of results.²⁵

Table 3 Summary of results for included studies reporting impact of ACB upon quality of life (n=4)

Anticholinergic Drug Scale (ADS) and quality of life

Two studies with sample sizes ranging from $n=112^{35}$ to $n=1793^{25}$ explored relationships between ACB and physical function using the ADS (shown in table 3). Both studies demonstrated moderate significant associations between increased ACB measured by the ADS and the physical domain of the SF36 (β - 0.30 (95% CI -0.10, -.51) $p<.01$)²⁵ and SF12 (est.

-7.48 (95% CI -12.57, -2.39) $p < .01$)³⁵ respectively. Neither study detected association between the ADS and the mental domains of the SF36 (β -0.07 (95% CI -0.28, 0.13) $p = ns$) or SF12 (Mean between group difference in SF12 scores -2.27 (95% CI -7.81, 3.27) $p = 0.43$)^{25,35}.

ARS and quality of life

Only one study explored relationships between ACB and quality of life using the ARS.²⁵ Results are detailed in table 3, but again a significant association with the physical, but not the mental, domains of the SF36 were identified.

Drug Burden Index- Anticholinergic sub scale (DBI-Ach) and quality of life

Only one study explored the relationship between DBI-ACh and quality of life²⁸ which demonstrated a small but significant relationship with reduced quality of life measured by the EQ5D (table 3).²⁸

Modified Clinician Rated Anticholinergic Score (mCRAS) and quality of life

Only one study explored the relationship between mCRAS and quality of life²³ which demonstrated significant association with the McGill Quality of Life score (table 3). Those with higher ACB scores reported poorer quality of life at follow-up.²³

Comparison of prognostic ability of ACB measures to predict future quality of life

Only two studies directly compared different ACB measures in the same population sample; Cossette (2017)²⁵ compared three measures (ACBS, ADS ARS), while Ie (2016)²⁸ compared the ACBS and DBI-ACH, to predict quality of life. The ACBS demonstrated the strongest associations in comparison to the ADS and ARS.²⁵ Ie (2016) demonstrated a stronger relationship using the DBI-ACH than the ACBS, however associations were very small (β - 0.095, $p < .05$).²⁸

GRADE Assessment

All GRADE assessments conducted for each ACB scale and outcome combination resulted in an assessment of 'Very Low', meaning that we have little confidence in the results and further studies will likely change the results. Quality was commonly downgraded due to serious concerns regarding study biases, inconsistency in results, indirectness, potential for publication bias and small effect sizes (see **supplementary file 1** for detailed GRADE assessments).

Discussion

This systematic review included 13 studies reporting the prognostic value of one or more ACB measures in relation to physical function or quality of life in older people. Seven out of ten studies reported a significant association between increased ACB and future impaired physical function, with the remaining studies showing a non-significant trend towards this. However, statistical and clinical heterogeneity prevents meta-analysis and our ability to recommend one measure above another. In relation to quality of life, four studies reported

the longitudinal relationships between ACB and quality of life amongst older people. Each study reported at least one significant association between ACB and quality of life, but again limited evidence prevents recommending one measure above another. At present, the evidence behind the ability of individual ACB measures to predict future physical function and quality of life is poor and does not permit informed decisions regarding which measure is best to assess ACB. We conclude that, in relation to older people, ACB shows a general trend towards impaired physical function and reduced quality of life but the question as to which ACB measure performs best remains unanswered.

In the review by Fox *et al.*, (2014)⁵ studies which failed to associate ACB and physical function often focused upon single domain aspects of function e.g. walking ability. Our study excluded such outcomes to focus upon global measures that are more comparable between populations. However, it has been suggested that specific domains of physical function such as gait may play important mediating roles between ACB and other adverse outcomes such as falls.³⁶ Research focusing upon the temporal relationship between ACB and global physical function, specific physical abilities and how these relate to other outcomes are required to advance our understanding of the complexities of this relationship.

Our findings support a general trend for increased ACB being associated with a reduction in quality of life; however, the evidence is limited by few studies and low study quality. The divergence in results between domains of quality of life, demonstrating greatest associations with the physical domain of quality of life than the mental domain, is not unique to ACB. Similar results were recently published in relation to associations between multi-morbidity

and quality of life where strong associations with physical, but not mental domains were also found.³⁷ Exploration of older peoples perspectives towards ACB and its impact upon quality of life is necessary to further understand what aspects, if any, ACB is perceived to impact upon, which may help explain this finding.

The number of, and variations between ACB measures, has been documented previously.^{13,38} Many were developed to target specific adverse outcomes, most commonly cognitive impairment and dementia.^{13,38} These may nevertheless be associated with the outcomes assessed in this review because cognitive impairment is associated with poorer physical function³⁹ and quality of life,⁴⁰ and because anticholinergics are well known to have many other adverse effects beyond cognitive impairment. Reliance upon expert rated anticholinergic potency is troublesome due to divergent views amongst clinicians.^{13,38} Conversely attempts to rate anticholinergic potency objectively is not without its limitations, not least discordance between measurable biological markers and symptoms of anticholinergic properties.^{13,38} Despite our intentions this present review cannot answer the question as to which ACB measure may be most suitable for predicting specific outcomes. The small number of studies, diverse range of outcome measures, and substantial differences in study characteristics means determining one ACB measure as being a better predictor of future physical function or quality of life is not possible. To improve prognostic research future research should be prospective longitudinal or case-control in design and sufficiently large, with sample size calculations appropriate for the outcome of interest and adjust for important confounding variables.

The strengths of this systematic review include its novelty in both focusing upon comparing ACB measures and being restricted to older people. Other strengths include its comprehensive search strategy using a validated search filter to identify relevant studies, reference list checks of all included studies and any seminal studies not included to ensure no eligible studies were omitted, and our decision to focus on longitudinal and case-control studies more suited to understanding adverse outcomes. However, this review also has some limitations. We did not include grey literature; while this can help avoid contaminating results with low quality non-peer reviewed evidence, we cannot say with certainty that its exclusion did not result in the omission of insightful and relevant papers. Finally, the small number of studies identified meant it was not possible to adequately assess for publication bias so we have to assume there is a possibility of this.

Conclusions and Implications

This systematic review identified 13 studies reporting the prognostic value of one or more ACB measures in relation to physical function or quality of life. The majority of studies show at least a general trend towards impaired function and reduced quality of life associated with increased ACB. At present the evidence behind individual ACB measures' ability to predict physical function and quality of life amongst older adults is poor and does not permit informed decisions regarding which is the best measure to use. Well-designed longitudinal studies are required to address this. However, the general consistency in our findings, alongside the wider body of evidence, suggests clinicians should continue to be aware of individual patients' anticholinergic burden and consider alternatives to anticholinergic medications where appropriate.

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419 **Supplementary file 1 PRISMA checklist, search strategy and GRADE assessments**

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Table 1 Characteristics of studies reporting association between ACB and physical function (n=10) and quality of life (n=4)

Study (Design)	Design	n	Age Years (Mean, SD)	Sex Male (n, %)	Country	Setting	Follow-up duration	ACB Measure	Function Measure	QoL Measure
Agar 2009 ²³	Prospective	461*	71.9 (12.0)	232 (50.0)	Australia	Palliative care	Death (mean 107 days)	CRAS	AKPS	MQoL
Brombo 2018 ²⁴	Retrospective	1123	81.0 (7.4)	494 (44.0)	Italy	Acute care (hospital)	1 year	ARS & ACBS	ADL (Katz)	-
Cossette 2017 ²⁵	Prospective	1793	74.4 (4.2)	853 (48)	Canada	Community	36 months	ACBS, ADS & ARS	-	SF36
Han 2008 ²⁶	Prospective	544	74.4 (5.2)	544 (100.0)	USA	Primary care clinic	1 year	mCRAS	IADL(OARS)	-
Hershkovitz 2018 ²⁷	Retrospective	869	83.4 (6.9) †	41 (20.2)	Israel	Geriatric rehabilitation centre	Discharge (mean NR)	ACBS	FIM	-
Ie 2017 ²⁸	Retrospective	426	78.6 (6.72)	48 (11.3)	USA	Care homes & Community	12 months	ACBS & DBI-Ach	-	EQ-5D
Kolanowski 2015 ²⁹	Prospective	99	86.1 (6.8)	22 (32.0)	USA	Post-acute care (hospital)	Discharge (mean NR)	ACBS	BI	-

Study (Design)	Design	n	Age Years (Mean, SD)	Sex Male (n, %)	Country	Setting	Follow-up duration	ACB Measure	Function Measure	QoL Measure
Koshoedo 2012 ³⁰	Prospective	105	79.0 (7.0)	29 (25.0)	UK	Orthopaedic rehabilitation unit	Discharge (mean 15 days)	ARS	BI	-
Koyama 2014 ³¹	Prospective	1429	83.0 (3.1)	0 (0.0)	USA	Community	5 years	ACBS	IADL (NS)	-
Landi 2014 ³²	Prospective	1490	83.6 (65.1-106.4) ‡	425 (28.5)	Italy	Nursing home	1 year	ARS	ADL (MDS-HC)	-
Lopez-Matons 2018 ³³	Retrospective	126	80.0 (6.7)	28 (27.8)	Spain	Geriatric clinic (hospital)	1 year	ACBS	BI	-
Pasina 2013 ³⁴	Retrospective	1323	79.9 (7.3) †	51 (49.7)	Italy	internal medicine and geriatric wards (hospital)	3 months	ARS & ACBS	BI	-
Sura 2016 ³⁵	Retrospective	112	Aged 65.00–79.0 (n=59) Aged ≥80 (n=53)	48 (42.9)	USA	Community	24 months	ADS	-	SF-12

ACB: Anticholinergic Burden, ACBS: Anticholinergic Cognitive Burden Scale, ADL: Activities of Daily Living, ADS: Anticholinergic Drug Scale, AKPS: Australian-modified Karnofsky Performance Status, ARS: Anticholinergic Risk Scale, BI: Barthel Index, CRAS: Clinician Rated Anticholinergic Score, DBI-Ach: Drug Burden

Index Anticholinergic sub-scale, EQ-5D: EuroQol 5D, FIM: Functional Independence Measure, IADL: Instrumental Activities of Daily Living, mCRAS: modified Clinician Rated Anticholinergic Score, MDS-HC: Minimum Data Set for Home Care, MQoL: MacGill Quality of Life Score, NR: Not Reported, NS: Not Specified, OARS: Older American Resources and Services, QoL: Quality of Life, SF-12: Short Form Health Survey 12, SF-36: Short Form Health Survey 36.

*461 participants recruited but Quality of Life analysis conducted with 304 participants who died during study follow-up; †Mean age for ACB users within sample; ‡ Median and IQR presented instead of mean (SD)

Fig. 1. QUIPS Risk of bias assessment of studies reporting association between ACB and physical function (n=10) and quality of life (n=4)

Physical Function

	Agar 2009	Brombo 2018	Han 2008	Hershkovitz 2018	Kolanowski 2015	Koshoedo 2012	Koyama 2014	Landi 2014	Lopez-Matons 2018	Pasina 2013
Study participation	High risk	Moderate risk	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Moderate risk	Low risk
Study attrition	Moderate risk	Moderate risk	Moderate risk	Moderate risk	High risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk
Prognostic factor	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk
Outcome	Low risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Confounding	High risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Statistical analysis	High risk	Moderate risk	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Moderate risk	High risk

Quality of Life

	Agar 2009	Cossette 2017	le 2017	Sura 2016
Study participation	High risk	Moderate risk	Moderate risk	Moderate risk
Study attrition	Moderate risk	Moderate risk	Moderate risk	Moderate risk
Prognostic factor	Moderate risk	Low risk	Low risk	Low risk
Outcome	Low risk	Moderate risk	Moderate risk	Moderate risk
Confounding	High risk	Moderate risk	Moderate risk	High risk
Statistical analysis	High risk	Moderate risk	Moderate risk	High risk

Table 2 Summary of results for studies exploring prognostic relationships between ACB scale and physical function (n=10)

Scale/ Outcome	Study	ACB (Baseline)	Physical Function (Baseline)	Statistical Approach	Results (Unadjusted)	Results (Adjusted)
ACBS (Range 0-3)						
ADL (≥1 ADL)	Brombo 2018 ²⁴	ACBS≤1: 381 (33.9%)	Any ADL: 542 (48.3%)	Multivariable logistic regression OR 95% CI (ACBS ≥1 versus ACBS=0)	2.38 (1.37,4.13) p=.002	2.77 (1.39, 5.54) p=.004*
		ACBS≥2: 348 (31.0%)				
BI (Range 0-100)	Kolanowski 2015 ²⁹	ACBS Mild: 81 (81.8%)	NR	Multiple linear regression β (SE)	NR	Mild: -3.41 (2.14) p= NS † Mod/sev: 5.76 (1.99) p=<0.05
		ACBS Mod/Sev: 25 (25.2%)				
	Lopez-Matons 2018 ³³	ACBS≥1: 26.4%	BI (Mean, SD): 88.9 (18.5)	Difference in the BI scores between exposed and unexposed patients Mean (SD) (95% CI)	-4.3 (3.3) (-10.8, -2.2)	-4.0 (4.5) (-12.9, 4.9) ‡
	Pasina 2013 ³⁴	ACBS≥1: 724 (58.8%)	NR	Correlation Pearson Coefficient	0.004 p = 0.91	NR
FIM (Range 18-126)	Hershkovitz 2018 ²⁷	ACB ≤1: 666 (76.6%)	60.5 (17.8)	Multiple linear regression β (SE)	NR	- 0.03 (0.85) p=0.02 §
		ACB≥2: 203 (23.4%)	56.3 (18.7)			

Scale/ Outcome	Study	ACB (Baseline)	Physical Function (Baseline)	Statistical Approach	Results (Unadjusted)	Results (Adjusted)
IADL (Range 0-8)	Koyama 2014 ³¹	ACBS Mean (SD): 1.6 (1.9)	NR	Multiple logistic regression OR (95 % CI)	1.11 (1.04, 1.18) p=NR	1.11 (1.04, 1.19) p=NR
ARS (Range 0-3)						
ADL (Range 0-28)	Brombo 2018 ²⁴	ARS≥1: 208 (18.5%)	ADL any: 542 (48.3%)	Multivariable logistic regression OR 95% CI	2.43 (1.26,4.68) p=.008	1.49 (0.60, 3.70) p=.38 *
	Landi 2014 ³²	ARS≥1: 721 (48.4%)	ADL Mean (SD): 15.4 (10.3)	Multivariable logistic regression OR (95% CI)	NR	1.13 (1.03, 1.23) p=.01 **
BI (Range 0-100)	Koshoedo 2012 ³⁰	ARS Median (IQR): 0 (0-1)	BI Median (IQR): 55 (40-60)	Poisson regression IRR (95% CI)	NR	0.97 (0.95, 0.99) p=0.008 ++
	Pasina 2013 ³⁴	ARS ≥1: 112 (9.1%)	NR	Correlation Pearson Coefficient	-0.06 p = 0.15	NR
CRAS/ mCRAS (Range 0-3)						
AKPS (Range 0-100)	Agar 2009 ²³	NR	AKPS (Mean, SD): 61.0 (13.8)	Logistic regression OR (95% CI)	NR	0.85 (0.81, 0.90) p= NR ‡‡
IADL (Range 0-8)	Han 2008 ²⁶	CRAS Mean (SD): 1.3 (1.5)	IADL Mean (SD): 6.5 (1.07)	Mixed effects linear regression Effect Estimate (95% CI)	0.16 (0.11, 0.25) p=.001	0.10 (0.04, 0.17) p= 0.001. ^{§§}

ACB: Anticholinergic Burden ACBS: Anticholinergic Cognitive Burden Scale, ADL: Activities of Daily Living, AKPS: Australian-modified Karnofsky Performance Status, ARS: Anticholinergic Risk Scale, BI: Barthel Index, CRAS: Clinician Rated Anticholinergic Score, FIM: Functional Independence Measure, IADL: Instrumental Activities of Daily Living, mCRAS: modified Clinician Rated Anticholinergic Score, nr: not reported, ns: not significant.

Adjustments:

- * Adjusted for age, sex, education, smoking, mini-mental state examination score, ACBS score at first follow-up, hypertension, coronary heart disease, renal failure, anaemia, infectious diseases.
- + Adjusted for gender, ethnicity, Charlson comorbidity index, clinical dementia rating, age, Apolipoprotein E status, education, previous weekly function performance.
- ‡ Adjusted for age, sex, body mass index, smoking, high blood pressure, diabetes, dyslipidaemia, heart disease, stroke, dementia.
- § Adjusted for age, sex, time from surgery to rehabilitation, admission albumin level, education, presence of caregiver, residency, mini-mental state examination score, admission FIM, ischemic heart disease, congestive heart failure, diabetes, hypertension, cardiovascular disease, depression, Parkinson's, chronic obstructive pulmonary disease.
- || Adjusted for age, race, years of education, smoking, physical activity, Charlson comorbidity index.
- ** Adjusted for schizophrenia, depression, cognitive performance scale score, age, sex, cumulative index rating scale, activities of daily living (baseline)
- ++ Adjusted for age, sex, Charlson comorbidity index, abbreviated mental test, total of other medications, Barthel index at admission
- ## Adjusted for time before death
- §§ Adjusted for age, race, education, living arrangement, follow-up year, baseline value of the outcome, activities of daily living, centre-epidemiological studies depression scale, smoking, alcohol use, Charlson comorbidity index and hypertension

Table 3 Summary of results for studies exploring prognostic relationships between ACB and quality of life (n=4)

Scale/ Outcome	Study	ACB (Baseline)	QoL (Baseline)	Statistical Approach	Results (Unadjusted)	Results (Adjusted)
ACBS (Range 0-3)						
SF-36 PCS (Range 0-100)	Cossette 2017 ²⁵	ACBS≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	-0.50 (-0.31, -0.68) p<.001 *
EQ-5D (Range 0-1)	le 2017 ²⁸	ACBS Mean (SD): 0.55 (0.87)	EQ-5D (Mean, SD): 0.82 (0.14)	Multiple linear regression β, SE (95% CI)	NR	0.006, .009 (-0.01, 0.02) p=NR †
ADS (Range 0-3)						
SF-36 PCS (Range 0-100)	Cossette 2017 ²⁵	ACBS≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	- 0.30 (-0.10, -.51) p<.01 *
SF-12 PCS (Range 0-100)	Sura 2016 ³⁵	Ach user: 17 (15.2%)	NR	Multiple linear regression Parameter estimate (95% CI)	NR	-7.48 (-12.57, -2.39) p<.01 ‡
ARS (Range 0-3)						
SF-36 PCS (Range 0-100)	Cossette 2017 ²⁵	ACBS≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	-0.43 (-0.69, -0.17) p<.01 *
mCRAS (Range 0-3)						
MQoL (Range 0-10)	Agar 2009 ²³	NR	McGill QOL Mean (SD): 6.0 (2.0)	Generalised linear models OR (95% CI)	NR	0.90 (0.85, 0.95) p=NR§
DBI-Ach (Range 0-3)						

EQ-5D (Range 0-1)	le 2015 ²⁸	DBI-Ach (Mean, SD): 0.05 (0.14)	EQ-5D (Mean, SD): 0.82 (0.14)	Multiple linear regression B, SE (95% CI)	NR	-0.09, .05 (-.19, .002) p<.05 _b
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Ach: Anticholinergic, ACB: Anticholinergic Burden, ACBS: Anticholinergic Cognitive Burden Scale, ADS: Anticholinergic Drug Scale, ARS: Anticholinergic Risk Scale, DBI-Ach: Drug Burden Index Anticholinergic sub-scale, EQ-5D: EuroQol 5D, mCRAS: modified Clinician Rated Anticholinergic Score, MQoL: MacGill Quality of Life Score, nr: Not Reported, QoL: Quality of Life, SF-12 PCS: Short Form Health Survey 12 Physical Component, SF-36 PCS: Short Form Health Survey 36 Physical Component.

Adjustments:

- * Adjusted for age, sex, education, income, living alone, frailty, number of comorbidities, modified mini-mental state examination and Geriatric Depression Scale.
- † Adjusted for age, sex, living with someone, income, no. of comorbidities, use of assistive devices, falls < 12 months, baseline DBI ACH, baseline DBI-SED, Baseline ACBS, no. regular medications, no. of BEERs list medications.
- ‡ Adjusted for predisposing factors such as age, race/ethnicity, gender, marital status, and education. Enabling factors included family income, health insurance coverage, region, and metropolitan status area (MSA). Need factors comprised of perceived general and mental health status, activities of daily living (ADL), instrumental activities of daily living (IADL), and cholinesterase inhibitors. The baseline PCS and MCS summary scores were used as additional need factors.
- § Adjusted for time before death



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Supplementary Material

ACB Prog Rev Function QOL S1 v2.docx

